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ENHANCED FUZZY EXPERT CONTROL FOR CANCER CHEMOTHERAPY DRUG DOSE SCHEDULING

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Abstract

In this paper, a multi-objective adaptive chemotherapy treatment model has been proposed to minimize the quantity of cancer cells and minimize the toxicity level due to drug doses after several fixed treatment cycles. A fuzzy expert control for chemotherapy scheduling (FECCS) has been proposed to find the optimal schedule. It consists of a mathematical model named Martin's model utilized to calculate the quantity of tumor cells, toxicity level, and drug concentration, a dose generator that generates dose schedules, and a fuzzy expert system that controls the output of the dose generator. Moreover, multi-objective optimization methods (Non-dominated sorting genetic algorithm-II and Particle swarm optimization) are employed and added to the developed FECCS to create Optimized-FECCS (OFECCS) and to optimize the dosing schedule while fulfilling both goals of this multi-objective optimal problem. In this research, NSGA-II performs better for maintaining average toxicity (objective-2), and PSO performs well for preserving the final count of cancer cells following the completion of the treatment period (objective-1). Remarkably, this approach surpasses previous literature in reducing cancerous cell count by the end of treatment.

Key words: Optimizer, Multi-objective optimization, NSGA-II, PSO, Cancer Chemotherapy.

Introduction

Cancer is a significant ailment that poses an enormous risk to human existence. By 2024, it is estimated that there will be 2,001,140 new cases of cancer and 611,720 cancer-related deaths in the United States, surpassing previous records (Siegel *et al.* 2023). Over the years, there has been a consistent rise in the prevalence of cancer in Bangladesh. In 2020, the International Agency for Research on Cancer (IARC) projected that the age-standardized occurrence rate (ASR) of cancer in Bangladesh was approximately 123.8 per 100,000 people (Sung *et al.* 2021). In Bangladesh, the prevalent forms of cancer are lung cancer, breast cancer, cervical cancer, oral cancer, and liver cancer. The mortality rate associated with this cancer continues to be an important issue. Around 94.2 deaths per 100,000 people in Bangladesh were attributed to cancer in 2018 (Sung *et al*. 2021).

Cancer is a condition characterized by the presence of malignant cells that communicate and collaborate with their environment in an intricate manner, forming a dense collection of cells called a tumor. This tumor hinders the formation of fresh blood vessels. Nevertheless, it is important to note that tumors are not present in several types of cancer, including leukemias, myeloma, and many kinds of lymphoma, that are beyond the main object of the present study.

In the medical industry, four major cancer treatment approaches exist: radiotherapy, surgery, biotherapy with agents, and chemotherapy. Death mainly occurs due to the spread of the cancerous cell to other parts of the body, and in that situation, surgical intervention becomes ineffective. Chemotherapy is a highly successful cancer treatment process that involves the administration of chemicals to the body to specifically target and eliminate cancer cells (Ghasemabad *et al*. 2022).

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The rapid proliferation of cells that characterizes cancer makes it particularly susceptible to the effects of chemotherapeutic medications. This is why chemotherapy is more potent compared to the other three methods of cancer treatment. Chemotherapy can be administered through different methods. It is frequently utilized either on its own or in conjunction with the procedures mentioned above (Alam *et al.* 2013a).

Chemotherapy treatment procedures try to keep tumor growth at a limit and destroy the cancerous cells by using low molecular weight drugs (Alam *et al.* 2013b). However, other living cells are also affected by chemotherapy. Traditional chemotherapeutic treatments are effective at destroying cells that reproduce rapidly, including those found in the bone marrow, digestive system, and hair follicles. However, these chemicals cannot manage to distinguish between normal cells and malignant cells (Beumer *et al.* 2012). Chemotherapy commonly leads to adverse reactions, including profound fatigue, muscle discomfort, myelosuppression (reduced production of blood cells, leading to immunosuppression), mucositis (an infection of the digestive tract), and alopecia (hair thinning) (Alam *et al.* 2013a, Alam *et al.* 2013b). These unwary conditions are termed toxicity.

Chemotherapy utilizes various categories of medications, including alkylating agents, anti-metabolites, anthracyclines, and topoisomerase inhibitors. They exhibit a correlation with toxicology, adverse consequences, and numerous other parameters. A correlation exists between the dosage of drugs administered and the proportion of eliminated cells after chemotherapy (Beumer *et al.* 2012). To minimize these toxic impacts of the drug and to maximize healthy cells, multiple techniques have been explored (Thurston and Pysz 2021). All these methods include dose scheduling. A chemotherapy dose schedule can be defined as the amount of dose that is needed to minimize treatment constraints like the number of malignant cells and toxicities after an inevitable treatment cycle. There exist some mathematical models for developing chemotherapy dose schedules. Among these, Martin’s model is used in this research.

Fuzzy expert systems have also been developed here, as medical knowledge is loaded with fuzziness in the field of cancer chemotherapy. It endeavors to emulate expert's suggestions to correctly determine the treatment schedule after the evaluation of the treatment response. The combination of such a system with a dose schedule generator and a chemotherapy model in a closed loop forms a fuzzy expert control for chemotherapy scheduling (FECCS). The most challenging part of this research is to develop the fuzzy expert system due to the complex mechanism of cancer chemotherapy.

Cancer chemotherapy is an intricate procedure that manages tumor growth by delivering a combination of drugs in a sequence of doses during chemotherapy. Oncologists have access to a diverse range of anti-cancer medications. These medications, because of their severe toxicity, have a wide range of adverse reactions that can vary from being aesthetically unappealing to very harmful, and even potentially life-threatening. Hence, the oncologist faces the difficult problem of creating an appropriate chemotherapy plan that minimizes tumor size and limits the adverse reactions of the medication to a manageable level, all while achieving certain treatment objectives. Due to the several objectives of cancer chemotherapy, every one of those being equally important, the issue of optimizing chemotherapy requires the application of multi-objective optimization methods. By using evolutionary algorithms, the multi-objective optimization method aids in generating a collection of best choices for FECCS in chemotherapy treatment procedures. Here, a non-dominated sorting genetic algorithm (NSGA-II) and particle swarm optimization (PSO) have been utilized. The generated solutions utilizing these algorithms will be able to minimize all the treatment objectives, like the final number of cancer cells and average toxicity, by satisfying all

the treatment constraints such as (i) tolerable maximum toxicity, (ii) maximum drug dose in a day, (iii) tolerable cumulative drug concentration and (iv) maximum allowable tumor cell number.

Furthermore, the following portions of this study are organized in the following manner: Section 2 provides a comprehensive summary of the most contemporary research on the schedule of cancer chemotherapy. Following this, Section 3 delineates the proposed approach, namely the fuzzy expert control for chemotherapy scheduling (FECCS) and elucidates the optimization process employed to refine the output membership functions of FECCS. The outcomes of this optimization are detailed in Section 4 and juxtaposed against those of existing methodologies. Finally, the study culminates with a conclusion in Section 5, summarizing the outcomes, and suggesting possible directions for subsequent research.

This literature review explores various optimization approaches applied to dose scheduling in cancer chemotherapy. Researchers have treated dose scheduling as a constrained optimization problem, aiming to minimize cancerous cells or tumor volume while adhering to treatment constraints (Alam *et al.* 2013a, Algoul *et al.* 2011a, Martin *et al.* 1990, McCall *et al.* 2008, Alam *et al.* 2013c, Algoul *et al.* 2011b, Swan 1986). Early works, such as Swan's logistic growth model (Swan 1986), focused on bilinear chemotherapeutic effects and dose administration frequency, while Martin and colleagues (Martin *et al.* 1990) studied intravenously administered drugs with Gompertzian tumor proliferation.

Later studies have brought forth a wave of innovation, introducing optimization techniques like genetic algorithms (McCall *et al.* 2008), particle swarm optimization (PSO) (Alam *et al.* 2013c), and multi-objective genetic algorithms (Algoul *et al.* 2011a, Algoul *et al.* 2011b). These approaches, with their ability to optimize dose schedules considering various treatment parameters and objectives, offer a promising future for cancer chemotherapy. Swarm intelligence-based optimization methods, like PSO, have demonstrated their adaptability in finding efficient chemotherapy schedules (Chen *et al.* 2020). They offer advantages in addressing multiple treatment objectives and allow for flexible treatment planning. Moreover, hybrid optimization techniques were developed to address constrained multi-objective optimization problems (Del *et al.* 2008). These methods offer promising avenues for developing personalized and effective chemotherapy regimens while minimizing adverse effects and maximizing treatment efficacy (Del *et al.* 2008). However, the quest for a method or system that can identify the scheduling day and the drug dose at the same time continues.

Recent studies underscore the transformative potential of artificial intelligence, particularly reinforcement learning (RL), in optimizing cancer treatment protocols. For instance, dynamic drug dosage control system leveraging Q-learning and Deep Reinforcement Learning are introduced (Lakshmi *et al.* 2024, Liu *et al.* 2022), while Alsaadi *et al.* (2023) proposes a fuzzy reinforcement learning method that enhances tumor eradication effectiveness compared to traditional approaches. Similarly, employment of multi-objective deep reinforcement learning to balance therapeutic efficacy with patient safety, demonstrating the importance of considering multiple health indicators during treatment (Huo and Tang 2022).

Another significant recent strategy is the incorporation of explainable AI (XAI) to improve trust in AI-driven medical decisions. The study by Lokare *et al.* (2024) emphasizes the necessity for transparent models in breast cancer treatment recommendations, which is crucial for fostering confidence among clinicians and patients alike. Furthermore, Kalweit *et al.* (2024) presents an innovative vision for automated adaptive dosing that continuously adjusts treatment based on real-time patient data, aiming to enhance the quality of care and survival rates. Additionally, machine learning-based approach by Debnath *et al.* (2024) demonstrates the effectiveness of multi-

objective particle swarm optimization in chemotherapy scheduling, emphasizing the need to minimize toxicity while effectively targeting cancer cells.

Materials and Methods

Optimized Fuzzy Expert Control for Chemotherapy Scheduling (FECCS: This research uses a growth model to find out the amount cancer cells and healthy cells, and the proposed fuzzy expert system is used to determine the dose schedule. The mathematical model was established by Martin and Teo (1994) and applied as the growth model. The amount of medication is mainly regulated by the fuzzy expert system, where the outcome of the growth model (number of healthy cells, cancer cells and drug-induced toxicity) is applied as the input into the FECCS. Further, FECCS determines the amount of drug dose by using expert opinion.

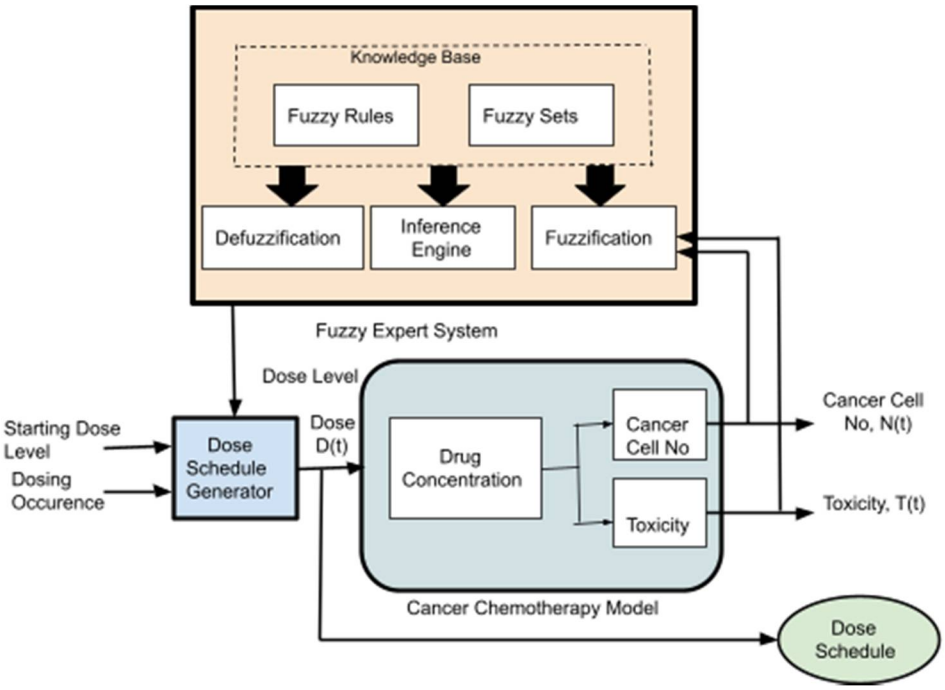

Fig. 1. Architectural components of Fuzzy Expert Control of Chemotherapy Scheduling (FECCS)

The first stage of this work is to develop a fuzzy expert control for chemotherapy scheduling (FECCS). Fig. 1 shows a graphical representation of the proposed FECCS with major functional components.

The proposed method calculates a dose plan using a dose schedule provider (fixed interval dosing system) that has been built based on clinical practices. The administered dose is subsequently used in the chemotherapy growth model to evaluate its impact on the immune system of a cancer patient. The feedback, consisting of the volume of cancerous cells and toxicity levels, is continuously incorporated into the suggested fuzzy systems to determine the subsequent

dosage for the individual receiving treatment. In this case, the fuzzy expert system is equipped with two inputs, namely the quantity of tumor cells and the level of toxicity, and one output, which is the daily dose level.

Input-1: Here, the starting quantity of tumor cells is considered 10^{10}. The feasible limit for the total quantity of tumor cells can be regarded to be between 0 and 10^{11}, taking into consideration a slight possibility of growth in the tumor population growth (Martin *et al.* 1990, Martin and Teo 1994). Fractional quantities are attainable in this work because the number of tumor cells is determined using the mathematical growth model. Based on previous records, the established limit for cancer cell quantity is set as 10^{-3} to 10^{11}, as the tumor cell number never falls below 10^{-3}.

In practice, experts may characterize the tumor cell as tumor size, which is why 'tumor size' is used as the first linguistic variable, where 'tumor cell number' decides the numerical value. For the linguistic variable 'tumor size,' four linguistic values are considered, they are: Very Small (VS), Small (S), Medium (M), Big (B), and Very Big (VB). Types and parameters of the membership function for tumor size are described in Fig. 2 and Table 1.

Table 1. Different types and parameters of the tumor size membership function.

Linguistic value	Type	Parameters
Very Small (VS)	Trapezoidal	[10^-3, 10^-3, 10^-2, 1]
Small (S)	Triangular	[10^-3, 10^0, 10^3]
Medium (M)	Triangular	[10^0, 10^3, 10^6]
Big (B)	Triangular	[10^3, 10^6, 10^9]
Very Big (VB)	Trapezoidal	[10^6, 10^8.5, 10^11, 10^11]

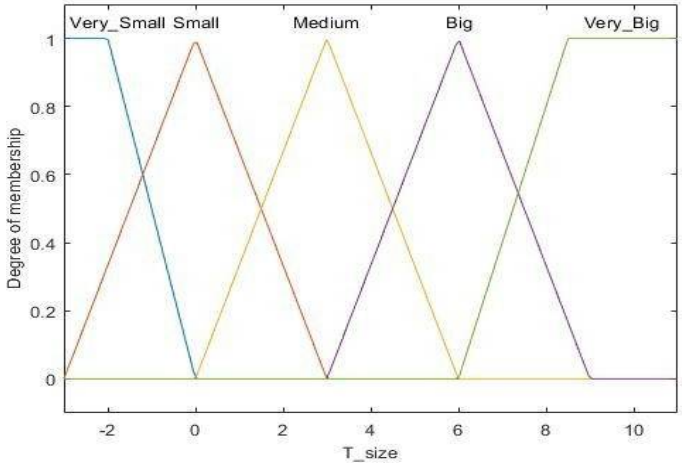

Fig. 2. Membership function, ranges and parameters for input 1 (Tumor Size).

Input-2: The range of linguistic variable 'toxicity' is taken 0 to 105, considering the maximum level of toxicity 100 per day. Linguistic values for toxicity are Very Low (VL), Low (L), Medium (M), High (H), Very High (VH). Types and parameters of the membership function for toxicity are described in Fig. 3 and Table 2.

Table 2. Types and parameters of the membership function for toxicity.

Linguistic value	Type	Parameters
Very Low (VL)	Trapezoidal	[0, 0, 3, 30]
Low(L)	Triangular	[0, 30, 60]
Medium(M)	Triangular	[30, 60, 90]
High(H)	Triangular	[60, 90, 120]
Very High (VH)	Trapezoidal	[90, 117, 120,120]

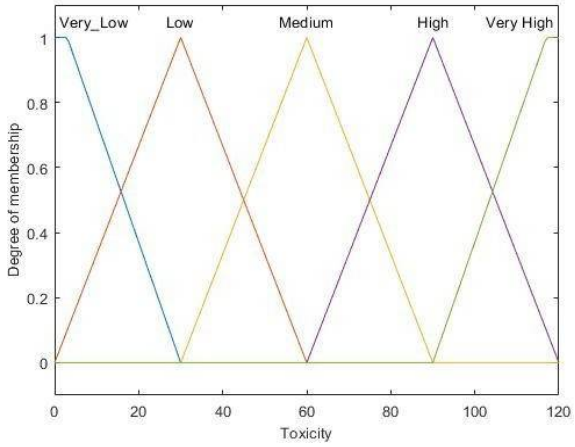

Fig. 3. Membership function, ranges and parameters for input 2 (Toxicity).

Output: Here, 'dose' is considered as the output linguistic variable and ranges from 10 to 50, where 10 is the threshold value for killing tumor cells, and 50 is the maximum allowable drug concentration. Linguistic values for dose are Very Very Low (VVL), Very Low (VL), Low (L), Medium(M), High (H), Very High (VH), and Very Very High (VVH). Types and parameters of the membership function for dose are described in Fig. 4 and Table 3. The range parameters of this output membership functions are optimized in Section 3.2, using either non-dominated sorting genetic algorithms or particle swarm optimization algorithms.

Table 3. Types and parameters for the dose membership function.

Linguistic value	Type	Parameters
Very Very Low (VVL)	Triangular	[10, 10, 16.67]
Very Low (VL)	Triangular	[10, 16.67, 23.33]
Low(L)	Triangular	[16.67, 23.33, 30]
Medium (M)	Triangular	[23.33, 30, 36.67]
High (H)	Triangular	[30, 36.67, 43.33]
Very High (VH)	Triangular	[36.67, 43.33, 50]
Very Very High (VVH)	Triangular	[43.33, 50, 56.67]

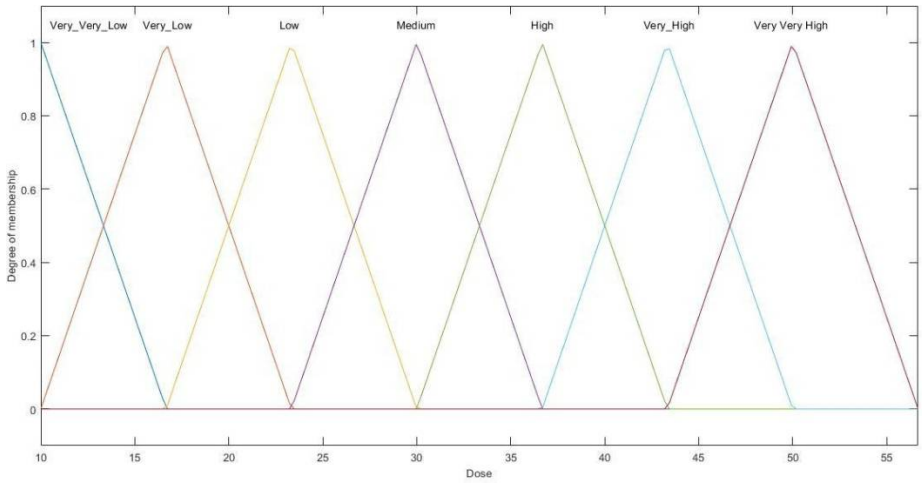

Fig. 4. Membership function, ranges and parameters for output (Drug dose).

Rule base: This proposed chemotherapy treatment aims to maintain minimum toxicity and remove tumors as early as possible. As there are no exact relationships among tumor size, toxicity, and dose level, the target is suggested to have a higher value of dose when the tumor size is big and also suggested to have a lower value of dose when the toxicity is high. So, by considering these conflicting targets, a rule base has been planned, which contains 21 rules for several combinations of input and output values suggested by experts. They are:

1. If tumor size is Very Small then Dose is Very Very Low.
2. If tumor size is Small and toxicity is Very Low then Dose is Medium.
3. If tumor size is Small and toxicity is Low then Dose is Low.
4. If tumor size is Small and toxicity is Medium then Dose is Very Low.
5. If tumor size is Small and toxicity is High then Dose is Very Very Low.
6. If tumor size is Small and toxicity is Very High then Dose is Very Very Low.
7. If tumor size is Medium and toxicity is Very Low then Dose is High.
8. If tumor size is Medium and toxicity is Low then Dose is Low.
9. If tumor size is Medium and toxicity is Medium then Dose is Low.
10. If tumor size is Medium and toxicity is High then Dose is Very Low.
11. If tumor size is Medium and toxicity is Very High then Dose is Very Very Low.
12. If tumor size is Big and toxicity is Very Low then Dose is Very High.
13. If tumor size is Big and toxicity is Low then Dose is High.
14. If tumor size is Big and toxicity is Medium then Dose is Medium.
15. If tumor size is Big and toxicity is High then Dose is Low.
16. If tumor size is Big and toxicity is Very High then Dose is Very Low.

17. If tumor size is Very Big and toxicity is Very Low then Dose is Very Very High.
18. If tumor size is Very Big and toxicity is Low then Dose is Very High.
19. If tumor size is Very Big and toxicity is Medium then Dose is High.
20. If tumor size is Very Big and toxicity is High then Dose is Medium.
21. If tumor size is Very Big and toxicity is Very High then Dose is Low.

Multi-objective optimization of FECCS using NSGA-II and PSO

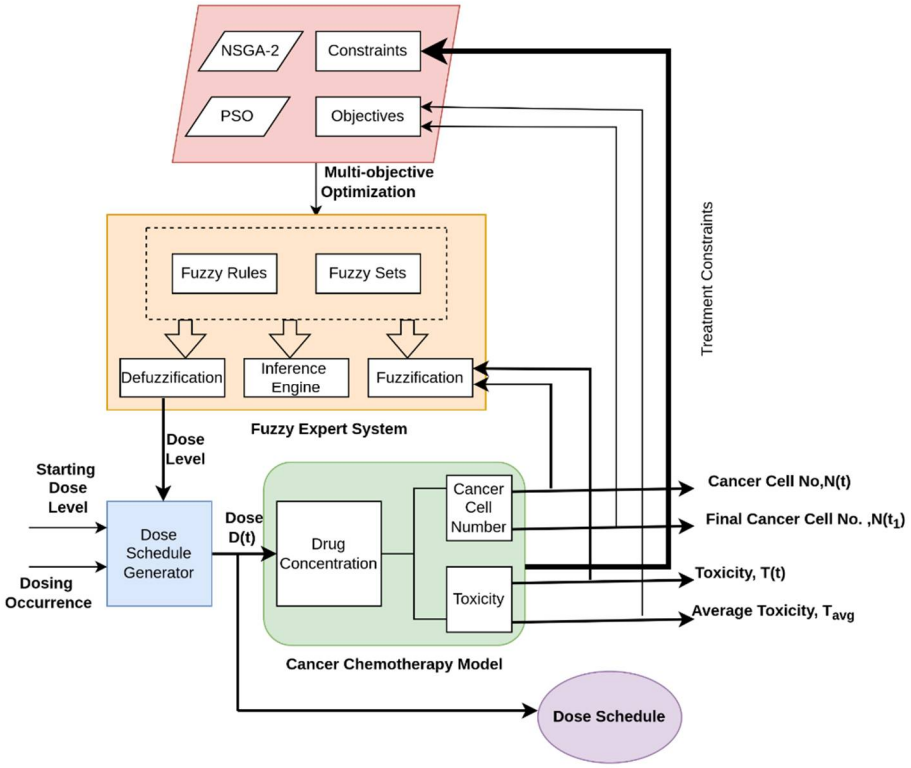

Fig. 5. The components for multi-objective optimization of OFECCS.

To enhance the performance of this Fuzzy Expert Control for Chemotherapy Scheduling (FECCS), a multi-objective optimization method using evolutionary algorithms (NSGA-II and PSO) has been developed in this section. Fig. 4 shows each component of the architecture of this Optimized Fuzzy Expert Control for Chemotherapy Scheduling (OFECCS). Here, only an extra block for multi-objective optimization is added, along with the components of the FECCS developed in the previous section (Fig. 1).

As we optimized membership functions of the output of fuzzy expert control (dose), there are some basic steps to follow. The following are the steps for providing optimized membership function parameters of non-dominated sorting genetic algorithm-II (NSGA-II):

Algorithm 1: Non-dominated Sorting Genetic Algorithm-II for Optimizing Membership Function Parameters

Input*: Population size, crossover rate, mutation rate, maximum number of iterations*

Output*: Optimized membership function parameters*

1: *Generate an initial population of candidate solutions based on the ranges presented in Table 5.*

2: *Assess the level of usefulness of each solution within the population.*

3: *Sort solutions into different levels based on their superiority over others.*

4: *Calculate the crowding distance for each possibility in each front. The crowding distance estimates how close a solution is to its neighbors in the objective space.*

5: *Choose candidates for the succeeding generation based on non-domination and crowding distance. Typically, the succeeding generation is created by selecting the best solutions from the fronts, giving priority to solutions in less crowded regions.*

6: *Apply crossover and mutation operators to the selected individuals to create offspring for the next generation.*

7: *Combine the offspring with the parent population to form the next generation.*

8: *Quit if the requirement for termination is satisfied, such as reaching the highest number of iterations (e.g., 50). Otherwise, return to step 2.*

We also used a particle swarm optimization algorithm to optimize the parameters of the output (dose) membership function of fuzzy expert control. The following are the steps for providing optimized membership function parameters of the Particle Swarm Optimization (PSO) algorithm (Chen *et al.* 2020):

Algorithm 2: Particle Swarm Optimization (PSO) for Optimizing Membership Function Parameters

Input*: Population size, velocity range, position range (Table 5), maximum number of iterations*

Output*: Optimized membership function parameters*

1: *Randomly initialize the position and velocity of each particle within the provided range.*

2: *Assess the level of suitability of each particle based on its position.*

3: *Revise the ideal position for each particle according to its current fitness level.*

4: *Determine the particle with the highest fitness score amongst all particles in the population and modify the global best position accordingly.*

5: *Revise the velocity and position of every individual particle.*

6: *If the termination criterion is met (maximum number of iterations reached, 50), stop. Otherwise, return to step 3.*

Here, the membership functions (mfs) of the Dose (output) of the FECCS have been optimized to minimize both tumor size and toxicity simultaneously through maintaining treatment constraints done by following steps:

1. The parameters of the membership function are taken as decision variables. Based on overlapping conditions and the variable range, the decision is defined and restricted.
2. After specifying decision variables, evolutionary algorithms (NSGA-II and PSO) are incorporated using MATLAB.

Membership functions (MFs) for the Dose (output of FECCS) defined earlier for FECCS in Table 3 are modified here. The parameters of the MFs (for Dose) are redefined to search for optimal MFs, considering 12 decision variables X2, X3, X4, X5, X6, X7, G1, G2, G3, G4, G5, and G6 for defining the parameters of MFs shown in the table below.

Table 4. Parameters of the membership function of dose in terms of variables along with previous values.

Linguistic value	Parameters before optimization	Parameters in terms of variable for optimization
Very Very Low (VVL)	[10, 10, 16.67]	[10, 10, 10+G1]
Very Low (VL)	[10, 16.67, 23.33]	[X2, X2+G2, X2+2G2]
Low (L)	[16.67, 23.33, 30]	[X3, X3+G3, X3+2G3]
Medium (M)	[23.33, 30, 36.67]	[X4, X4+G4, X4+2G4]
High (H)	[30, 36.67, 43.33]	[X5, X5+G5, X5+2G5]
Very High (VH)	[36.67, 43.33, 50]	[X6, X6+G6, X6+2G6]
Very Very High (VVH)	[43.33, 50, 56.67]	[X7, X7+G7, X7+2G7]

Some conditions are applied to provide overlapping MFs, keep a valid relationship between the parameters of MFs, and specify the decision variable ranges in Table 5.

$$X2 <= 10 + G1 \quad (1)$$

$$X3 <= X2 + 2G2 \quad (2)$$

$$X4 <= X3 + 2G3 \quad (3)$$

$$X5 <= X4 + 2G4 \quad (4)$$

$$X6 <= X5 + 2G5 \quad (5)$$

$$X7 <= X6 + 2G6 \quad (6)$$

Table 5. Ranges of decision variable.

Decision variable	X2	X3	X4	X5	X6	X7	G1	G2	G3	G4	G5	G6
Upper limit	12	17	26	33	38	45	7	6	8	6	6	6
Lower limit	10	16	23	30	36	43	2	4	5	5	5	5

For experimenting with this proposed Fuzzy Expert Control for Chemotherapy Scheduling and to optimize its output membership functions (mfs), a small length of treatment procedure (120 days) has been considered to determine the objectives and other performance. All the outputs obtained from our experiments are presented and analyzed in Section 4.

Results and Discussion

The experiments for optimizing the fuzzy expert control for chemotherapy scheduling were conducted using MATLAB programming (MathWorks 2022). The numbers of cancerous cells were converted into logarithmic values to facilitate representation. Moreover, the newly generated parent population was retained for subsequent generations, ensuring that superior solutions were preserved throughout the process.

The meticulousness of the research is evident in the definition of all the ranges for selecting the parameters of membership functions, as outlined in Tables 4 and 5. The maximum generation number (for NSGA-II) and iteration number (for PSO) were set at 50, reflecting the thoroughness of the optimization process. For both optimization algorithms, the maximum population and particle number were carefully set at 30.

In the beginning, we used membership function values from Fig. 4 for the fuzzy expert systems output (drug dose amount suggestion). Further, after executing the OFECCS among 50 generations and applying 50 iterations for both NSGA-II and PSO, it provides optimized membership function values represented in Figs. 6 and 7.

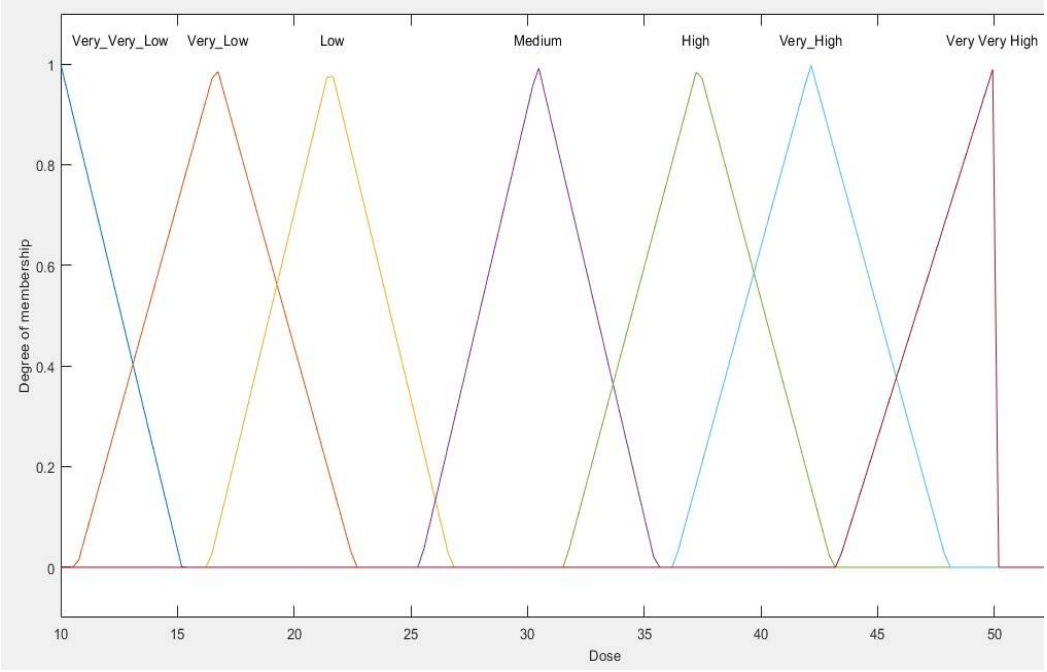

Fig. 6. Optimized membership functions generated from NSGA-II, after 50 iterations.

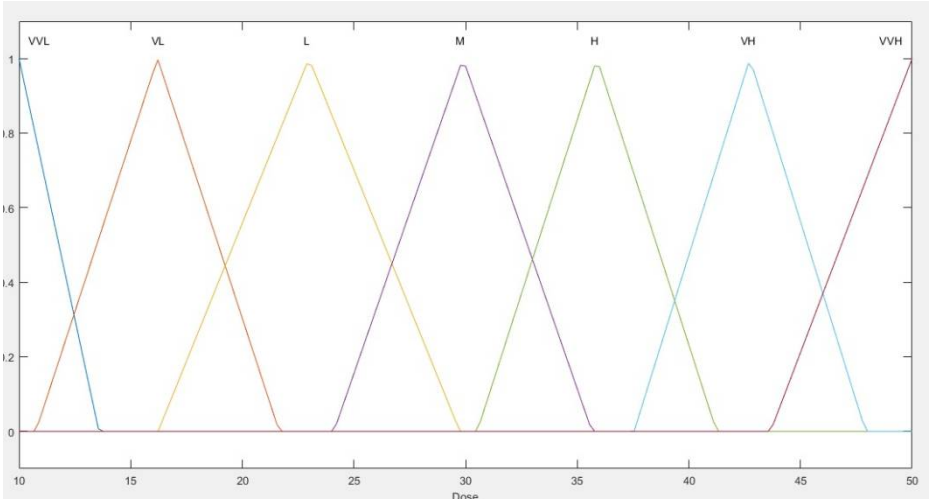

Fig. 7. Optimized membership functions generated from PSO, after 50 iterations.

Using these optimized membership functions, fixed-interval drug doses are generated and tabulated in Table 6. Moreover, Figs. 8, 9, and 10 also describe the doses generated by unoptimized and optimized fuzzy expert control for the chemotherapy scheduler.

Table 6. Drug dose schedules generated from FECCS, OFECCS (NSGA-II), and OFECCS (PSO) with fixed intervals of 14 days (about two weeks).

Week	Day	Drug dose (D)		
		FECCS	OFECCS (NSGA-II)	OFECCS (PSO)
0	1	40	40	40
2	15	44.73	40.66	41.95
	16			
4	29	37.41	36.30	39.49
	30			
6	43	32.69	30.46	35.698
	44			
8	57	30.84	31.10	31.58
	58			
10	71	29.93	30.64	29.52
	72			
12	85	27.27	28.59	26.33
	86			
14	99	23.93	24.88	23.62
	100			
16	113	22.01	22.79	21.78
	114			

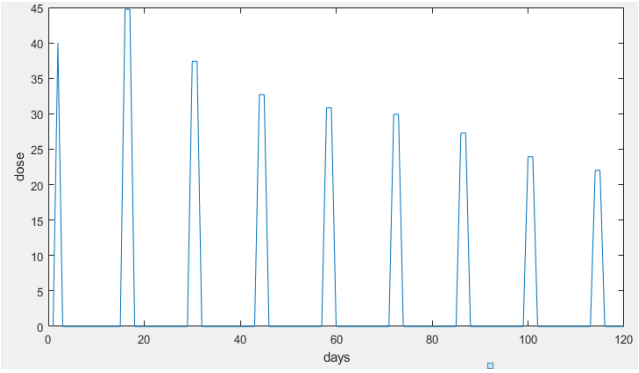

Fig. 8. Drug dose schedule generated by fuzzy expert control for chemotherapy drug dose scheduler (FECCS).

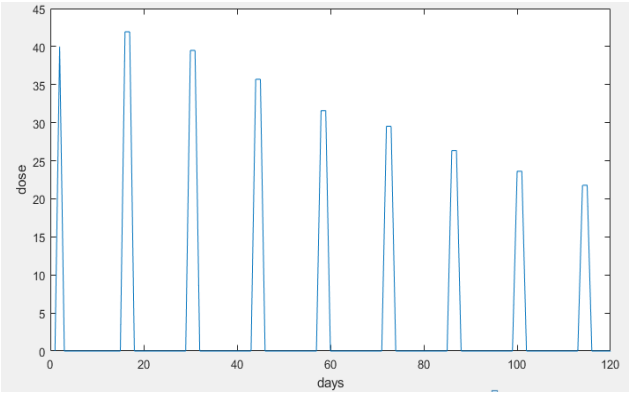

Fig. 9. Drug dose schedule generated by optimized (using PSO) fuzzy expert control for chemotherapy drug dose scheduler (OFECCS).

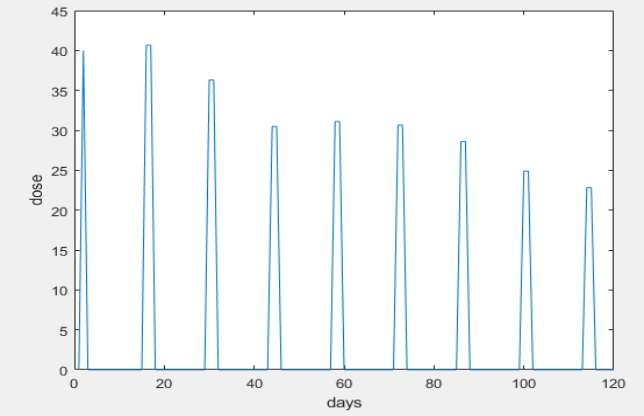

Fig. 10. Drug dose schedule generated by optimized (using NSGA-II) fuzzy expert control for chemotherapy drug dose scheduler (OFECCS).

The impact of suggested drug doses is delineated in Fig. 11 and 12. A comparison between total cancerous cell reduction by these three methods (FECCS, OFECCS using NSGA-II, and OFECCS using PSO) has been represented in Fig. 11. It is apparent from the figure that OFECCS using PSO is the most capable method for reducing the cancerous cell from the patient's body while taking care of its toxic reaction. FECCS is the second-best performer here, and OFECCS using NSGA-II performed worst in reducing cancerous cells. Furthermore, Fig. 12 represents the generated toxicity for applying the suggested drug dose by three methods (FECCS, OFECCS using NSGA-II, and OFECCS using PSO). According to previous studies (Faisal *et al.* 2023), the toxic side effects generated from injecting chemotherapy drug doses should be under 100. However, applying chemotherapy drug dose generated from FECCS provides toxicity, which is more than 100. At the same time, the toxicity generated from OFECCS (using PSO or NSGA-II) maintained the expected results, never exceeding a toxicity level of more than 100.

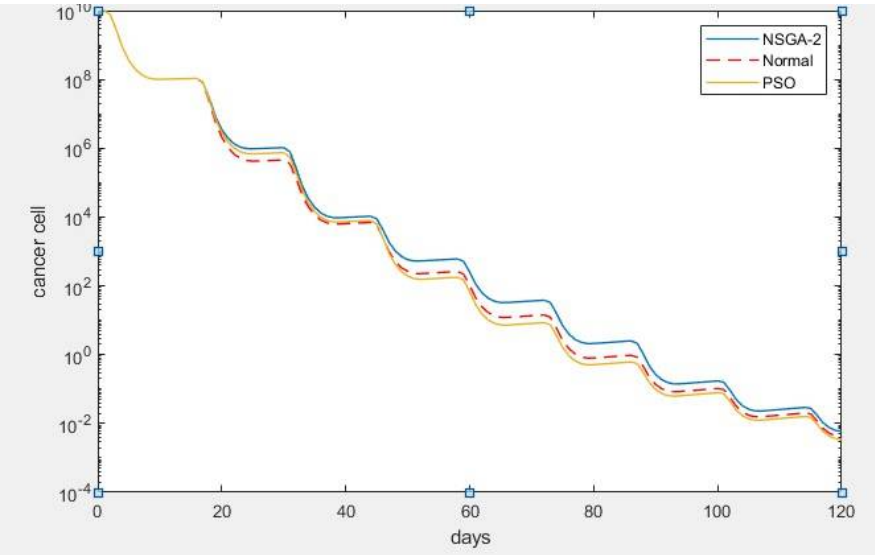

Fig. 11. Cancerous cell reduction by not optimized FECCS (using NSGA-II or PSO) and optimized fuzzy expert control for chemotherapy drug dose scheduler (OFECCS).

Table 7 describes a comparison between fuzzy expert control for chemotherapy scheduling and optimized fuzzy expert control for chemotherapy scheduling (using NSGA-II and PSO). It presents maximum and minimum drug doses, maximum and average toxicity, and the number of cancerous tumor cells following the completion of the treatment. At the end of the 120-day therapy, OFECCS utilizing PSO showed superior performance in dealing with malignant cells. However, it is worth noting that its average toxicity level is considerably greater compared to other methods. The proposed FECCS reduced a massive number of cancerous cells, which performed better than OFECCS using NSGA-II, but it provides maximum toxicity, which is more than 100. According to previous studies, we should not provide any amount of drug dose, which can be the reason for toxicity of more than 100. Furthermore, in case of generating toxic side effects, OFECCS using NSGA-II performs better than all other methods, but it performs worse in terms of destroying cancerous cells.

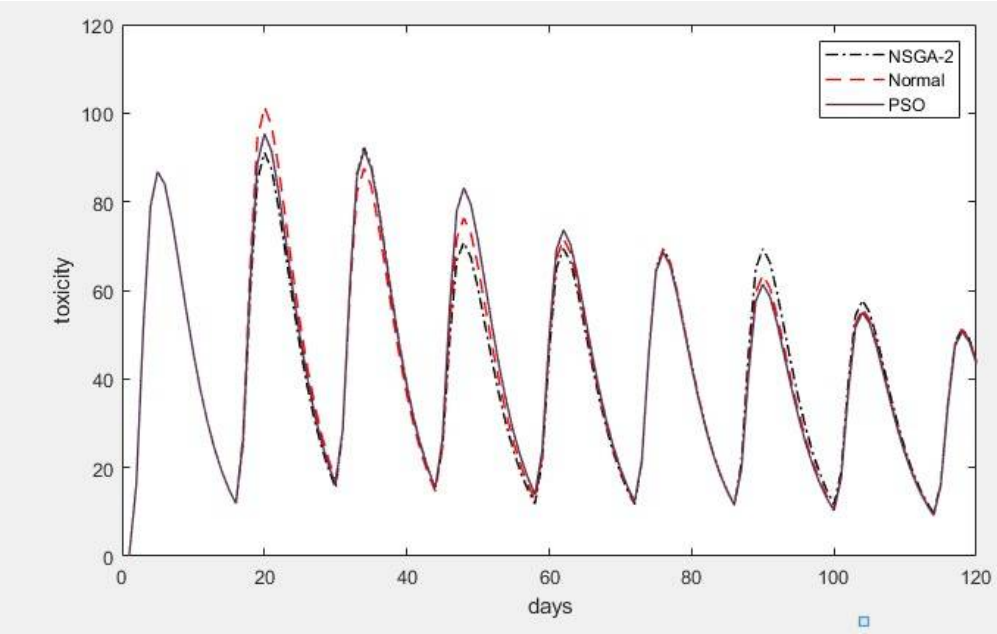

Fig. 12. Toxicity generated by Unoptimized FECCS and optimized (using NSGA-II or PSO) fuzzy expert control for chemotherapy drug dose scheduler (OFECCS).

Table 7. Comparison among FECCS, OFECCS using NSGA-II and OFECCS using PSO, in terms of drug dose amount, toxicity and reduced tumor cells.

Case	Drug dose		Maximum toxicity	Maximum tumor cell no.	Objective-1	Objective-2
	Maximum	Minimum			Tumor cell no. after 120 days	Average toxicity
FECCS	44.73	22.01	101.39	10^10	0.0042	42.88
OFECCS (NSGA-II)	40.67	22.80	88.72	10^10	0.0073	42.32
OFECCS (PSO)	41.94	21.78	95.34	10^10	0.0035	43.07

Table 8 presents a comparative analysis of the effectiveness of the suggested methodology (FECCS, OFECCS using NSGA-II, and OFECCS using PSO) with other optimal control approaches used in prior research that are similar in nature. The comparison is conducted using the performance index and the final count of malignant cells post-treatment, taking into account toxicity. The proposed method was unequivocally successful in achieving the objective of cancer treatment, as evidenced by the impressive performance indices of 28.26, 28.11, and 28.33, respectively, for FECCS, OFECCS using NSGA-II, and OFECCS using PSO. However, the presence of cancerous cells existence in size is minimal.

Table 8. Comparison of efficacy between the suggested methodologies (FECCS, OFECCS with NSGA-II, and OFECCS with PSO) with the currently available chemotherapeutic techniques for drag scheduling.

Dose scheduling methods	Performance Index (PI)	Final number of cancerous cells
Tan *et al*. 2002	17.99	1.53 × 10^4
Tsai *et al.* 2013	24.74	18.0
Algoul *et al.* 2011a	24.92	15.0
El-Garawany *et al.* 2017	25.51	~8 (8.34)
Khadraoui *et al*. 2016	27.56	~1 (1.078)
Karar *et al*. 2020	27.63	~1 (0.806)
FECCS	28.26	~1 (0.0042)
OFECCS (NSGA-II)	28.11	~1 (0.0073)
OFECCS (PSO)	**28.33**	~1 (0.0035)

Conclusion

As cancer stands as a formidable adversary to society, effective treatment strategies, such as chemotherapy, to combat its ravages are needed. Our proposed system, Fuzzy Expert Control for Chemotherapy Scheduling (FECCS), emerges as a promising solution in this battle against cancer; it provides schedules of chemotherapy drug doses with the expert's opinion. As there can be errors in making decisions for the parameters and ranges of membership functions, we have optimized membership function parameters through multi-objective optimization procedures (i.e., NSGA-II and PSO) by introducing Optimal Fuzzy Expert Control for Chemotherapy Scheduling (OFECCS). Through its optimization capabilities, OFECCS facilitates the generation of an optimal dose schedule tailored to individual patient needs. It enhances the precision of dose optimization by fine-tuning all parameters of the output membership function dose. Utilizing the NSGA-II algorithm within OFECCS yields superior outcomes in mitigating drug toxicity while employing PSO, which demonstrates efficacy in reducing cancerous cell counts. Notably, both FECCS and OFECCS surpass existing methods, underscoring their efficacy and potential to significantly improve cancer treatment outcomes. By integrating optimization algorithms, FECCS and OFECCS offer new hope in the quest for more effective and personalized chemotherapy regimens, ultimately advancing the fight against cancer and improving patient care.

In the future, we can focus on integrating machine learning techniques for more accurate prediction models, considering additional clinical parameters, exploring real-time patient monitoring technologies, conducting clinical validation studies, and ensuring scalability and interoperability for clinical implementation.

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